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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/603,385	06/24/2003	Fen Zhang	41812-8001.US00	3044

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	10/603,385	ZHANG, FEN	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/06/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election of Species

Claims 1-20 are generic to a plurality of disclosed patentably distinct species comprising: a growth factor, a ligand, an immunologically active molecule, an anti-microbial protein, an anti-inflammatory protein, an anti-neovascularization protein, a protease inhibitor, a hair growth promoting factor, an antiviral protein, a bioactive antibody, a bioactive single chain antibody, PDGF-beta, KGF, KGF-2, FGF-2, EGF, TGF-a, epiregulin, VEGF, NGF, GM-CSF, TGF-b, IGF-I, HGH, a bactericidal/permeability-increasing protein, a protein, a polypeptide, a peptide, a defensin, a collectin, Granulysin, Protegrin-1, SMAP-29, lactoferrin, Calgranulin C, interleukin-1 receptor antagonist, soluble TNF receptor, soluble CTLA4, interleukin-10, endostatin, angiostatin, soluble VEGF receptor, TIMPs, PAI-1, PAI-2, ecotin, wnt, sonic hedgehog, soluble herpes viral receptor Hve A, herpesvirus entry mediator C (HveC), the herpesvirus immunoglobulin-like receptor (HIgR), and soluble herpes surface protein gD.

Claims 1-20 are generic to a plurality of disclosed patentably distinct species comprising: a membrane, a matrix, a gel, a web, a net, and a material capable of performing the function of a membrane. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed. Should Applicant elect a natural membrane, a further election among the species of amnion membrane, cerebral dura mater membrane, fascia lata membrane, and pericardium membrane is required.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Norbert Stahl on 6/28/04 a provisional election was made with traverse to prosecute the invention of "growth factors" and "amniotic membrane". Affirmation of this election must be made by applicant in replying to this Office action. Nonelected species are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The combination of the species "growth factors" and "amniotic membrane" is anticipated in claims 1-5, 7-13, 16-18, and 20 by Faulk et al (Lancet 1(8179): 1156-1158, 1980), and is rendered obvious in claims 6, 14, 15, and 19 are rendered obvious by the combination of Faulk with Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996) and Sakuragawa (US Patent 6117676, issued 9/12/00). As such, no non-elected species are rejoined.

Claims 1-20 are under consideration in this Office Action.

Priority

Priority is claimed in the first line of the specification to provisional application 60/391,550, filed 6/24/2002. The effective filing date of the application is considered to be 6/24/2002.

Specification

The specification is objected to because it contains numerical citations but does not disclose the cited references. See for example page 39, lines 31 and 33 wherein references 28-36 are cited, and compare to the list of cited references at pages 1 and 2, which contains only 25 references. Deletion of the citations is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15 are indefinite because the recited method steps are not concordant with the purpose set forth in the preamble. The preamble requires delivery of a molecule to a patient, but the method steps require only administration of cells capable of delivering the molecule. There is no step in which the molecule is delivered, so the claims are incomplete.

Claims 9 and 16-20 are indefinite because it is unclear what are the metes and bounds of "a nutrient poor environment found on the skin". The specification does not define "nutrient-poor environment" in the context of the skin, stating only that "the dermal surface is generally considered to be a nutrient-poor environment" (see paragraph 160). The term "poor" in this context is a relative term that modifies the parameter of nutrient abundance. Because "poor" is not defined by the claims, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 12 and 13 are indefinite because they recite "the function of a membrane" without proper antecedent basis. Membranes have a variety of functions including acting as partitions or acting as a substrate for cellular growth or taxis, thus one of skill in the art cannot know to which membrane function "the function of a membrane" refers.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and compositions for delivering a growth factor to a wound in the skin of a patient by administering to the wound site amniotic epithelial cells that secrete the growth factor, does not reasonably provide enablement

for obtaining desired effects other than wound healing, for delivering molecules other than growth factors, or for methods of delivering molecules to sites other than the site of cell administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods and compositions for delivering a molecule to a patient comprising administering to the patient amniotic epithelial cells, wherein said cells are capable of delivering the molecule. The specification defines the term patient as the recipient of the molecule to be delivered regardless of the purpose of such delivery (detailed description paragraph 74), so the claims are not limited to medical treatment. The claims embrace methods and compositions intended to provide desired effects such as therapeutic, cosmetic, prophylactic, and diagnostic effects. While no pending claim requires the use of engineered epithelial cells to deliver products encoded by exogenous genes, this use is embraced by the instant claims, and the specification is largely directed to this method. The recited therapeutic, cosmetic, and prophylactic effects are not limited in breadth. As a result they embrace effects as diverse as the treatment and cure of HIV, glioblastoma, cystic fibrosis, and wound healing. There is no recited nexus between the site of cell administration and the site of molecule delivery, so the claims embrace systemic molecule delivery, as well as molecule delivery to specific target organs such as the brain, kidneys, and lungs through application to the skin. Additionally, the claims are not limited to the delivery of

peptides or polypeptides, but embrace the delivery of any molecule without limitation to any site without limitation for the purpose of eliciting any desired effect.

The specification provides no working example of the delivery of any molecule to a patient through the use of the amniotic epithelial cells. No guidance is presented as to how to deliver any type of molecule other than a secretable gene product. No guidance is presented with regard to how many amniotic epithelial cells must be transfected with what type of expression construct to achieve the appropriate level of expression of any specific gene product for any specific desired effect. Instead the specification teaches a working example in which an amniotic membrane is stripped of its epithelium, reconstituted with Madin-Darby Canine Kidney (MDCK) cells that stably express PDGF-beta, and applied to a rabbit chronic wound model. Accelerated healing is reported. However, as noted above, the claims are in no way limited to wound healing, but embrace delivery of any molecule to any site of any patient for the diagnosis or treatment of any cosmetic or medical condition. The specification provides no guidance at all regarding how much expression is required of any of the 52 species of molecules recited in claim 7 for any therapeutic, cosmetic, or prophylactic purpose, e.g. for the treatment of HIV or glioblastoma. As noted above, the specification also fails to provide any guidance as to how to use the claimed invention to delivery any molecule other than a polypeptide or a peptide.

Claim embodiments relating to obtaining therapeutic, cosmetic, and prophylactic effects by delivery of genetically modified cells that express a desired polypeptide or peptide are not adequately enabled due to a lack of guidance. This art was recognized

as highly unpredictable at the time of filing, and the specification fails to provide the guidance that is missing from the prior art. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). With specific regard to ex vivo therapy using retroviral vectors, Verma taught that expression of transgenes was shut off within five to seven days, even in animals lacking a functional immune system. Verma also points out that the search for an appropriate enhancer-promoter combination is a case of trial and error for each given type of cell. See page 240, column 2, lines 10-1, and sentence bridging columns 2 and 3. Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21.

However, the prior art teaches that wound healing may be facilitated by the delivery to a wound of expression vectors encoding growth factors. See e.g. US Patent 5962427, claims 1-14, and especially claims 6-11. Furthermore, the prior art teaches that epithelial cells may be transfected with expression vectors encoding growth factors, applied to a membrane, and administered to a wound to improve healing. For example, Eming (Invest. Dermatol. 105(6): 756-763, 1995) taught that grafts of keratinocyte monolayers retrovirally modified to overexpress PDGF-A aided in tissue regeneration when administered to the skin of immunodeficient (athymic) mice. See abstract, and page 757, column 2, fourth full paragraph. These results were reproduced by Eming et al (Biotech. Bioeng. 52: 15-23, 1996), see abstract and page 19, column 1, first full paragraph, and column 2, first full paragraph. As a result methods of improving wound healing by administration of epithelial cells modified to express growth factors is considered to be enabled.

However, the prior art and specification do not enable the treatment of wounds, or any other therapeutic, prophylactic, cosmetic, or diagnostic effect by delivery of molecules other than growth factors, as there is no guidance whatsoever as to how to use amniotic epithelial cells to deliver any molecule other than a peptide or polypeptide. The specification also provides no guidance at all regarding treating such diverse diseases as HIV, glioblastoma, or cystic fibrosis with any molecule, although these treatments are embraced within the metes and bounds of the claims. The specification also provides inadequate guidance as to how to improve wound healing with molecules other than growth factors. Wound healing is recognized as a very complex process

involving intricate interactions between a variety of cell types, structural proteins, growth factors, and proteinases. (Stadelmann, W.K., et al., Am J Surg 176(Supp 2A):26S-38S, (1998)). Some of the factors involved in wound healing may affect more than one aspect of the process. So, when a therapeutic regime is contemplated for impaired wound healing, the various process involved in wound healing, i.e. inflammation, angiogenesis, mesenchymal cell chemotaxis and proliferation, epithelialization, wound contraction, collagen synthesis, and remodeling, must be critically considered, and an accurate diagnosis of the factors impairing wound healing must be made. See Eming et al (Cells, Tissues, Organs (2002) 172(2): 105-117) page 106, column 2, first full paragraph. The specification provides no guidance as to the appropriate level of expression of any gene product, nor how to obtain and limit expression within such limits. For example, although the specification suggests the use of anti-inflammatory proteins, it provides no guidance as to how much expression of any anti-inflammatory protein is therapeutic. This is a critical omission in view of the fact that it is recognized in the specification and the prior art that inflammation is a normal part of wound healing. Indeed, Eming (2002) taught that impairment of inflammation could cause inadequate angiogenesis, mesenchymal cell chemotaxis and proliferation, epithelialization, wound contraction, collagen synthesis, and remodeling. It follows that overexpression of anti-inflammatories could actually impede wound healing.

The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific treatment regimens that achieve a therapeutic, cosmetic,

diagnostic, or prognostic effect. However, the specification does not provide such guidance and fails to provide any correlation between vectors, cells comprising vectors, dosage amounts, therapeutic genes other than growth factor genes, and any specific disease or condition treatable by the nucleic acids or cells comprising such as disclosed in the instant specification. Without such guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-12, and 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakuragawa (US Patent 6117676, issued 9/12/00), as evidenced by Uchida et al (J. Neurosci. Res. 62: 585-590, 2000).

This rejection is directed to a generic embodiment of the rejection which does not require amniotic membrane, rather than to the elected embodiment that requires an amniotic membrane.

Sakuragawa taught methods of transfecting human amniotic epithelial cells with adenoviral or plasmid vectors, and disclosed methods of using the cells to treat

lysosomal storage diseases by implanting in the subcutis cells encapsulated in a plastic film. See column 3, lines 51-67; column 4, lines 1-16 and 25-35; and column 5, line 25 to column 6, line 17. Inasmuch as the cells of Sakuragawa are composed of molecules, Sakuragawa teaches the delivery of molecules to a patient. Regarding the elected species of molecule to be delivered, i.e. a growth factor, Uchida et al (J. Neurosci. Res. 62: 585-590, 2000) taught that amniotic epithelial cells were known prior to the time of filing to secrete the growth factor NGF. See abstract.

With regard to claim 12, note that the instant specification does not define the term "synthetic membrane" so it has been given its broadest reasonable interpretation. In this interpretation, the plastic film of Sakuragawa is considered to be a supporting synthetic membrane.

The intended use limitations in claims 3-6 and 9 are not given patentable weight because the specification does not teach how these intended uses further limit the active method steps or the structure of the recited cells or molecules. Because Sakuragawa teaches all the steps of the method, as well as the structures of the claimed cells and molecule, Sakuragawa anticipates these claims.

In any case, even if the intended use language of claims 3-6 was given patentable weight Sakuragawa would still be anticipatory for the following reasons. Amniotic epithelial cells were known prior to the time of filing to secrete the growth factor NGF. So, regardless of whether or not the method of Sakuragawa is enabled for gene therapy, the cells are deemed to deliver to the surrounding dermal cells a detectable amount of NGF in view of Uchida. Note that claims 6, 14, 15, and 19, which

require an exogenous polynucleotide, recite no nexus between the polynucleotide and the delivered molecule, so there is no requirement for the delivered molecule to be encoded by the polynucleotide. Instant claims 3-6 are drawn to the method of claim 1, wherein the molecule is useful for achieving a desired effect (claim 3), and wherein the cells deliver an amount of the molecule sufficient to achieve that effect (claims 4-6). The claims do not limit the nature of the desired effect, so it is interpreted broadly. For example, the desired effect could be interpreted as "sufficient to allow detection of the molecule." This is a reasonable interpretation inasmuch as the molecule could serve as a diagnostic marker for the presence of the cells. Uchida teaches that amniotic epithelial cells secrete detectable amounts of NGF, so absent evidence to the contrary, the method of Sakuragawa would result in delivery to skin cells of detectable amounts of NGF.

Claim 9 is drawn to the method of claim 1 wherein the cells must be capable of delivering the molecule in a nutrient-poor environment on the skin. Absent evidence to the contrary, the capacity of amniotic epithelial cells to deliver proteins is an inherent characteristic independent of whether or not the environment is nutrient-poor, so the cells of Sakuragawa are considered to meet the limitations of this claim. " See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed

products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. Furthermore, every protein in an amniotic epithelial cell can be considered to be delivered to the skin merely as a consequence of administering the amniotic epithelial cell to the skin, there is no requirement for any metabolic activity such as secretion.

Claims 1-5, 7-13, 16-18, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Faulk et al (Lancet 1(8179): 1156-1158, 1980) as evidenced by Uchida et al (J. Neurosci. Res. 62: 585-590, 2000).

Faulk taught a method of treating burned skin by application of amniotic basement membrane comprising amniotic epithelial cells. See abstract, and page 1156, column 2, first two paragraphs. Inasmuch as the cells of Faulk are composed of molecules, Faulk teaches the delivery of molecules to a patient. Regarding the elected species of molecule to be delivered, i.e. a growth factor, Uchida et al (J. Neurosci. Res. 62: 585-590, 2000) taught that amniotic epithelial cells were known prior to the time of filing to secrete the growth factor NGF. See abstract.

The intended use limitations of claims 3-5 and 9 are not given patentable weight because the specification does not teach how these intended uses further limit the

active method steps or the structure of the recited cells or molecules. Because Faulk teaches all the steps of the method, as well as the structures of the claimed cells and molecule, Faulk anticipates these claims.

Claims 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996).

This rejection is directed to a generic embodiment of the rejection which does not require amniotic epithelial cells and an amniotic membrane.

Eming taught a composition comprising keratinocytes genetically modified to secrete a biologically effective amount of PDGF-A, wherein the cells were attached to a silastic support. See abstract, and page 17, column 1, second paragraph under the heading "Grafting". Thus Eming anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulk et al (Lancet 1(8179): 1156-1158, 1980), in view of Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996) and Sakuragawa (US Patent 6117676, issued 9/12/00).

Faulk taught a method of treating wounded skin by application of amniotic basement membrane comprising amniotic epithelial cells. See abstract, and page 1156, column 2, first two paragraphs.

Faulk did not teach amniotic epithelial cells engineered to include an exogenous polynucleotide.

Eming taught a method of promoting growth and vascularization in a wound by delivering PDGF-A to a patient. Epithelial keratinocytes were genetically modified to express PDGF-A, and were attached to a supporting membrane and administered to the skin of an immunodeficient (athymic) patient, resulting in improved growth and vascularization in the wound. See abstract, and page 17, column 1, second paragraph under the heading "Grafting".

Sakuragawa taught that amniotic epithelial cells could be transfected by either plasmid or adenoviral vectors, and that amniotic epithelial cells do not express HLA-A, B, C and DR antigens and do not cause rejection reactions or topical inflammation even when transplanted allogeneically. See column 2, lines 9-13 and 27-39; column 3, lines 51-67; column 4, lines 1-16 and 25-35; and column 5, line 25 to column 6, line 17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Faulk by transfecting the amniotic epithelial cells with the vector of Eming. One would have been motivated to do so because Eming shows that delivery of PDGF-A by transfected epithelial cells attached to a membrane results in tissue regeneration. One would have selected amniotic epithelial cells because Sakuragawa teaches that these cells can be conveniently transplanted allogeneically

without rejection due to the absence of cell surface HLA class II antigens, and a much diminished amount of HLA class I antigens. This would allow study of the healing process in immune-competent animals without instigation of inflammation beyond that which is ordinarily associated with wound healing. Also, Sakuragawa demonstrates that these cells can be transfected by means of viruses or plasmids, and suggests their use in therapeutic applications involving administration of the cells to skin. Finally, using cells on an amniotic membrane, as taught by Faulk, eliminates the step of applying cells to a synthetic membrane, thereby simplifying the procedure of Eming.

Thus the invention as a whole was prima facie obvious.

Claims 1-6 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulk et al (Lancet 1(8179): 1156-1158, 1980), in view of Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996), Sakuragawa (US Patent 6117676, issued 9/12/00), and Pollock et al (US Patent 6191269, issued 2/20/2001).

The teachings of Faulk, Eming, and Sakuragawa are discussed above and can be combined to render obvious methods and compositions for delivering molecules to a patient by genetically modifying amniotic epithelial cells to produce the molecule, and administering the amniotic epithelial cells on an amniotic membrane. These references teach the use of plasmid or adenoviral vectors for transfection of amniotic epithelial cells.

These references do not teach the use of retroviral, lentiviral, adeno-associated virus, or cosmid vectors.

Pollock taught that plasmids, cosmids, retroviral vectors, lentiviral vectors, adenoviral vectors, and adeno-associated viral vectors could be used interchangeably as expression vectors in eukaryotic cells. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). As such, it would have been obvious to substitute retroviral, lentiviral, adeno-associated virus, or cosmid vectors for the plasmid or adenoviral vectors of Sakuragawa.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax

number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.